Design, Fabrication and Characterization of Self Nano-Emulsifying Drug Delivery System for Biopharmaceutical Optimization

A Synopsis Submitted To

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AIM & OBJECTIVE:

- Solubility study of drug in oil, surfactant and co-surfactant.
- Screening of oil, surfactant, and co-surfactant for emulsifying ability.
- To formulate Semi- solid SNEDDS for filling into the hard gelatin capsule.
- To characterize the prepared self micro-emulsifying formulation for globules size and zeta potential.
- Comparison of In-vitro and in-vivo study of prepared formulation with plain drug.

INTRODUCTION:

Self nano emulsion is an isotropic mixtures of oils, surfactants, co-surfactant and sometimes containing co-solvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. Oral route may be a problem for drug mole cules which exhibit poor aqueous solubility.[1]To get absorbed from the gastrointestinal tract; a drug has to be sufficiently soluble, because, with some exceptions, passive diffusion of dissolved drug molecules from high to low drug concentration is the driving force of drug absorption. Different physicochemical and physiological properties determine the reasons for poor drug absorption, which are poor water solubility, low membrane permeability, carrier mediated drug efflux, drug metabolism, and pharmacological interactions.

Different formulation approaches like micronization, solid dispersion, [3] and complexation with cyclodextrins have come up.[4] indeed in some selected cases, these approaches have been successful but they offer many other disadvantages.

- The main problem with micronization is chemical/thermal stability. Many drugs may degrade and loose bioactivity when they are micronized by conventional method.
- For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires particular facilities and processes, leading to high production cost.
- Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents.

- SNEDDS: SNEDDSs are isotropic mixtures of oils, surfactants, and co-surfactant and sometimes containing co-solvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds.
- Advantage of SNEDDS over conventional emulsion:
  - Thermodynamically stable.
  - Ease formulation technique.
  - Globule size.
  - SNEDDS can be formulated in conventional dosage form eg. Tablet, capsule etc.

LITERATURE REVIEW:

- Chun-Han Chen et al **2015**: Self-nanoemulsifying drug delivery systems ameliorate the oral delivery of silymarin in rats with Roux-en-Y gastric bypass surgery. Roux-en-Y gastric bypass (RYGB) is a popular surgery to reduce the body weight of obese patients. Although food intake is restricted by RYGB, drug absorption is also decreased. The purpose of this study was to develop novel self-nanoemulsifying drug delivery systems (SNEDDS) for enhancing the oral delivery of silymarin, which has poor water solubility
- Maulic Patel et al **2011**: A review novel lipid based formulation of poue solubility drugs.
- Nisha GS et al **2011:** Studied carbamazepine solubility by self micro emulsification formulation and its characterization.
- Setthacheewakul S. **2010:**,Studied the pseudo ternary phase diagram to optimized SEDDS for liquid and pellet form of Curcumin contained 70% mixtures of two surfactants: Cremophor EL and Labrasol (1:1), and 30% mixtures of oil: Labrafac PG and Capryol 90 (1:1), The Curcumin-SMEDDS in liquid and pellet formulations rapidly formed fine oil-in-water micro emulsions, with particle size ranges of 25.8–28.8 nm and 29.6–32.8 nm, Optimized formulation showed 16 fold higher in vitro rate and extend of release of Curcumin than unformulated Curcumin. Pellet formed were 6 month stable under intermediate and accelerated condition.
- Kamble, V. **2010**: Review of self emulsifying drug delivery system. Discussed introduction, formulation, evaluation, factors affecting, advantages and disadvantages and application of SEDDS.

- Nekkanti V. **2010:** Solid SEDDS of candesartan cilexetil were developed for filling into the hard gelatin capsules. The solid carrier used was microcrystalline cellulose and colloidal silicon dioxide. The formed capsule showed the faster rate of drug release than the marketed formulation in discriminate dissolution media
- Dixit AR. **2010: S**MEDDS has been developed to enhance diffusion rate and oral bioavailability of valsartan. SMEDDS was prepared using Capmul MCM (oil) Tween80 (surfactant) and polyethylene glycol 400 (co surfactant). The particle size distribution, zeta potential, and polydispersity index were determined and were found to be 12.3 nm, −0.746, and 0.138, respectively. The area under curve and time showed significant improvement as the values obtained were 607 ngh/mL and 1 h for SMEDDS in comparison to 445.36 and 1.36 h for market formulation suggesting significant increase ($p<0.01$) in oral bioavailability of valsartan SMEDDS. The prepared formulation showed improved in AUC than the marketed formulation.
- Shi S. **2010:** Cinnarizine loaded in lipid emulsion to modify the pharmacokinetic, tissue distribution and safety of cinnarizine were prepared by high-pressure homogenization. Cinnarizine loaded emulsion (CLE) remains stable over 18 month The CLE showed significant higher AUC and lower clearance and distribution volume than those of solution form. The shelf life of cinnarizine in lipid emulsion was estimated to be 1471.6 days at 40C which is much longer compared with 19.8 days in aqueous solution.
- Yosra S.R. Elnaggar et al **2009** :Tamoxifen citrate is an antiestrogen for peroral breast cancer treatment. The drug delivery encountersproblems of poor water solubility and vulnerability to enzymatic degradation in both intestine and liver.
- Paradkar AR. **2009:** Evaluated the extended delivery of felodipine for management of hypertension studied the SNES containing model lipophilic drug, felodipine (FLD), to improve its solubility. Formulation contains Miglyol 840 as oil, Cremophor EL (as surfactant), and Capmul MCM (as co surfactant).The release was controlled by the use of Aerosil 200. The gelled SNES further encased within the hydrophobic Gelucire 43/01 (Gel) coat to extend the release of felodipine. Caprol PGE-860 (CAP) was added to this coat as a release enhancer.
- Cui J. **2009**: Significantly Increased the solubility (21 mg/g) of poorly water soluble drug Curcumin by SEDDS with optimized formulation composition 57.5% surfactant (emulsifier OP: Cremophor EL = 1:1),30.0% co-surfactant (PEG 400) and 12.5% oil

(ethyl oleate) with good stability to formulation after 3 months period. It was found that the in vitro dissolution study showed more than 95% of Curcumin in SMEDDS could be dissolved in pH 1.2 or pH 6.8 buffer solutions in 20 min, however, less than 2% for crude Curcumin in 60 min. and SMEDDS could significantly increase the oral absorption of Curcumin compared with its suspension in mice.

- Balakrishnan P. et al. **2009**: Enhanced the solubility and bioavailability of poorly water-soluble Co-ezyme Q10 (CoQ10) with optimized SEDDS formulation consist bof 65% (v/v) Labrasol, 25% (v/v) Labrafil M 1944 CS and 10% (v/v) Capryol 90 of each excipient with fixed level of CoQ10 at 6% (w/v) with minimum mean droplet size (about 240 nm) showed SEDDS have significantly increased the Cmax and area under the curve (AUC) of CoQ10 compared to powder ($P < 0.05$).
- Balakrishnan P. et al. **2009**: Enhanced oral bioavailability of Dexibuprofen by a novel solid Self-emulsifying drug delivery system (SEDDS), the solid form of SEDDS by spray drying liquid SEDDS with an inert solid carrier Aerosil 200. The liquid SEDDS was consisted of Dexibuprofen, Labrasol, Capryol 90 and Labrafil M 1944 CS. the result showed that SEDDS gave significantly higher AUC and Cmax than did Dexibuprofen powder ($p<0.05$)
- Xi J. **2009:** Four formulations, where OA was fixed at the concentration of 20 mg/g, were prepared utilizing Sefsol 218 as oil phase, Cremophor EL and Labrasol as primary surfactants, and Transcutol P as co surfactant. The developed SNEDDS showed increased in vitro release of OA either in water or in simulated gastric fluid. Meanwhile, it also improved the oral bioavailability of OA by prolonging the retention time of OA in rat plasma.
- Bachhav YG. **2009**: Prepared SMEDDS of BCS class II antidiabetic agent, glyburide (GLY) were prepared consist of Capryol 90 as oil phase, Tween 20 (surfactant), Transcutol P (co surfactant), the glyburide SMEDDS exhibited globule size of 133.5nm and polydispersity index of 0.94. It was observed that the GLY undergo significant degradation in developed SMEDDS.
- Liu Y. **2008**: Studied the optimize and characterize an Oridonin SMEDDS formulation using central composite design (CCD) to investigate the influence of factors (oil percentage and surfactant to co-surfactant ratio (Sur/Co-s ratio)) on the responses including droplet size, polydispersity, equilibrium solubility and in situ intestine absorption rate.

- Sarasija S. **2008**: Developed the SEDDS to enhance the dissolution and oral absorption of poorly soluble Curcumin and evaluated for its physicochemical properties, anti-antigenic and anti-inflammatory activity in colitis induced rat model. This formulation was characterized for enhancement in solubility, in vitro dissolution, surface morphology, IR, DSC and X-ray studies. Optimized formulationSF2 showed 13.0% and 75.3% release at the end of 1 hr and 12 hrs whereas pure Curcumin showed 0.12% and 6.23% release in 1 hr and 12 hrs respectively. SEDDS formulation (SF-2) significantly attenuated the degree of colitis caused by administration of DSS as compare to pure Curcumin.
- Kale A, and Patravale V. **2008**: Studied design and Evaluation of SEDDS of Nimodipine with various mixtures of excipients (LCTP) Labrasol containing 80%Transcutol-P and (P 497) Plurol, Oleique CC 497 with 30% w/v of constant value of nimodipine. It was found that relative bioavailability of NM in SEDDS was significantly higher than NM suspension, NM oily solution, NM micellar solution in rabbits.
- Yi T. **2008:** developed the new solid SMEDDS for nimodipine consist of ethyloleate, Labrasol, Cremophor RH 40, and nimodipine. The solid SEDDS prepared by spray drying with dextran as solid carrier. Particle size obtained in the range of41.3±3.1 and 44.1±4.5 for liquid SEDDS and solid SEDDS respectively. Both formulations showed similar AUC and Cmax after oral administration in to the rabbit. NM SEDDS successfully withstood the stability testing.
- Patil et al. **2007**: Evaluated in vitro and in vivo parameters of SMEDDS of simvastatin formulated using a 1:1 (V/V) mixture of diesters of caprylic/capric acids and polyglycolyzed glycerides with varying concentrations of poly-oxy castor oil andC8/C10 mono-/diglycerides. SEDDS containing 9.1% (m/m) simvastatin and 23.0% (m/m) of each excipient showed minimum mean droplet size (124 nm) and optimal drug diffusion. This test formulation showed significant reduction in plasma CH and TG (around 5-fold and 4-fold, respectively), while HDL-CH concentration was markedly higher (2-fold) compared a reference simvastatin suspension formulation after oral administration for 21 days of study.
- Wei L et al. **2007:** Developed a novel osmotic pump tablet which includes Gelucire44/14, Lutrol F68, Transcutol P, Silicon dioxide, Mannitol, citric acid, and sodium hydrogen carbonate. The Self-emulsifying osmotic pump tablet (SEOPT). The complete release of Carvedilol under the osmotic pressure of Mannitol was

observed.DSC, IR and XRD experiment showed that Carvedilol was amorphous in the tablet core the results of dissolution experiment showed that the release of Carvedilol from self-made SEOPT was controlled and complete and its profile was close to zero order release. The in vitro and in vivo correlation was good (r = 0.9725).

- Date AA. **2007:** Developed self nanoemulsifying drug delivery system (SNEDDS) to overcome the problem of Cefopodoxime proxetil, like high dose antibiotic having pH dependent solubility. The optimized CFP SNEDDS needed surfactant content less than 40% and yield nanoemulsion of mean globule size 170nm not affected by the pH of the body fluid. The optimized formulation contains Capryol 90 as oil phase, Cremophor EL surfactant phase the optimized SNEDDS released CFP completely within 20min irrespective of the pH of dissolution medium.
- Tang J. **2006**: Studied the SEDDS for Improving Oral Absorption of Ginkgo Biloba Extracts having optimized formulation consisted of 45% Tween 80, Cremophor EL35 (1:1, w/w), 10% 1, 2-propanediol, and 45% ethyl oleate and it was found that after oral administration of GBE as SEDDS or tablets to fasted dogs, the relative bioavailability of SEDDS for bilabolide and ginkgolide A and B was 162.1, 154.6, and 155.8% compared with the reference tablets, respectively.
- Li et al. **2005**: Evaluated the effects of combined use of two nonionic surfactants on the characteristics of oil-in-water micro emulsions generated from flurbiprofen-loaded pre-concentrates using Campul PG-8, Tween 20 and Cremophore EL. A number of pre-concentrates were selected based on the phase diagrams. Flurbiprofen loading in pre-concentrates was tested at 0%, 1%, 2.5% and 5% (w/w) and they found that the use of surfactants in pre-concentrates showed the promise in generating desired self emulsifying micro emulsions.
- Patil et al. **2004**: Studied the gelled SEDDS of Ketoprofen using Captex 200(oil), Tween 80(surfactant), Campul MCM (co-surfactant) and Silicon dioxide (gelling agent) and the effect of concentrations of co surfactant and gelling agent on emulsification process and in vitro drug diffusion by 32 factorial design. Multiple regression analysis data and response surfaces obtained showed that liquid crystal phase viscosity increased significantly with increasing amount of silicon dioxide which in turn caused an increase in average droplet size of resultant emulsion and slower drug diffusion.
- Kim Y, Young K. **2000**: Studied the SEDDS of Indomethacin for enhancing the absorption after oral and rectal administration to rats by using Tween 85 (surfactant)

and Ethyl oleate (oil). They selected the SES with 30 % of Tween 85 and 70 % of ethyl oleate (w/w) as the optimized formulation. After an oral administration of the SES containing IDM and IDM suspension, (IDM was suspended in methylcellulose), 22.5 mg: kg as IDM, to rats, the area under the plasma concentration–time curve from time zero to the last measured time in plasma, 12 h (AUC0–12 h) was significantly greater (57% increase) in the SES, suggested that oral absorption of IDM increased significantly by the SES

- Pouton, CW. **1997**: Discussed the strategies used for formulation of SEDDS, methods used for assessment of efficiency of emulsification and practical considerations regarding the use of SEDDS for enhancement of the bioavailability of drugs from the gastrointestinal tract. Self-emulsification may be associated with liquid crystal formation and that low frequency dielectric spectroscopy may be of considerable use in understanding the factors leading to self-emulsification.
- Craig et al. **1994**: Prepared series of SES mixtures comprising Imwitor 742 and Tween 80 and their self-emulsifying properties studied using a method of visual examination and low frequency dielectric spectroscopy. This study suggests that self emulsification may be associated with liquid crystal formation and that low frequency dielectric spectroscopy may be of considerable use in understanding the factors leading to self-emulsification.

RATIONALE OF STUDY:

Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. A rate limiting step for the absorption of these drugs is often their solubilisation in the gastrointestinal tract. These drugs are classified as class II drug by biopharmaceutical classification system (BCS). Oral route is the easiest and most convenient way of non-invasive administration. Oral drug delivery systems being the most cost-effective have always lead the world wide drug delivery market.

So therefore we have to develop system and to increase the solubility of drug.

PLAN OF WORK:

1. **Literature Review:**
2. **Selection of drug and excipients:**
3. **Experimental work:**
4. **Preformulation study:**

- **Drug Authentication:**
  - Melting point:
  - IR Spectroscopy
  - UV Spectroscopy:
- **Drug excipient Compatibility Studies:**
  - UV spectroscopy
  - IR spectroscopy
- **Determination of the saturation solubility of Drug in oil and surfactant.**
- **Selection and screening of potential Nano emulsion component**
- **Screening of oils, surfactant and co-surfactant**
- **Standard Curve of Drug**
- **Determination of Nano emulsion existence region & Construction of pseudo-ternary phase diagrams:**

5. **Preparation of selfnano emulsifying drug delivery system (SNEDDS)**
6. **Characterization of the SNEDDS:**
   - In Vivo and vitro study
   - Transmission electron microscopy (TEM)
   - Scanning electron microscopy (SEM)
7. **Reconstituted properties of SNEDDS:**
   - Visual observation
   - Globule size determination
   - Zeta potential analysis
8. **Result and Discussion:**
9. **Summary and Conclusion:**

DURATION OF WORK:

- The self nano emulsifying drug delivery drug delivery development by using ternary phase diagram and and evaluation by appropriate method.
- Ultra-violet Spectrophotometer, FTIR instrument
- NMR Instrument, Mass Spectrometer and various other instruments, apparatus and chemicals will be used for the experiment.
- Their activity will be evaluated by using proper models

Sr. No.	Activity	Tentative Duration (months)
1	Literature Review	06
2	Solubility study and construction of ternary diagram	08
3	Preparation of nano emulsion and characterization of reconstituted properties	12
4	Pharmacological screening of prepared nano emulsion (In vivo study) and in vitro study	04
5	Compilation, interpretation of data and writing of Thesis	06
	Total	36

RESEARCH OUTCOME

Biologically active drug formulation compounds are useful for the human health life. Drug formulation ompounds contributed to the development of society from a biological and industrial point of view as well as to understand life process and in efforts to improve the quality of life. The present study will be carried out systematically and with strategic planning like use cemix software, Pseudo tarnary diagram method, Therefore, chances of getting breakthrough drug molecules are sure, which may be patented or published in highly, reputed journals.

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